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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/040,010	Applicant(s) MILLS ET AL.	
	Examiner Shaojia A Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *21 and 26-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,8,12*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's claim for domestic priority to provisional applications Serial No. 60/260062 and 60/267296 under 35 U.S.C. 119(e) is acknowledged.

Election/Restrictions

Applicant's election with traverse of the invention of Group I, Claims 1-20, and 22-25, and the invention of the species of Y-27632 as the compound recited in claim 1, guanine nucleoside dissociation inhibitor (GDI) as a compound that inhibits GTP binding to RhoA enzyme recited in claim 9, sodium nitroprusside as the compound recited in claim 10, NOR-1 as the compound recited in claim 11, submitted October 6, 2002 is acknowledged.

It is noted that guanine nucleoside dissociation inhibitor (GDI) is considered to be a genus, not a specified individual active compound.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 21 and 26-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-20, and 22-25 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-20, and 22-25 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular compound such as Y-27632 disclosed in the specification (see Figure 2 for example) in co-administering the particular compounds such as sodium nitroprusside or NOR-1 employed in methods for particular treatments herein, does not reasonably provide enablement for the administration of any compounds represented by "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation" alone or in combination with any compounds represented by "a compound that inhibits binding of GTP to RhoA enzyme" or "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", or "a second compound which potentiates the effects of nitric oxide", for the claimed methods of treating male or female sexual dysfunction.

These recitations, "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" in these claims, are seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of treating male or female sexual dysfunction.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on any compounds represented by "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" employed in the claimed methods of treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in the instant claims, is admonished in *University of California v. Eli Lilly and Co.* 43

USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation", "a compound that inhibits binding of GTP to RhoA enzyme", "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", and "a second compound which potentiates the effects of nitric oxide" recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides those particular compounds of formula for each kind of functional compounds for the claimed method of treatment herein (see the specification 14, 15 and 30).

Thus, the instant specification fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph, since it fails to provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of

monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treating male or female sexual dysfunction, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a male human) any compound represented by "a compound which attenuates RhoA and/or RhoB kinase activity to sexual stimulation" alone or the *combination* of any compounds represented by "a compound that inhibits

binding of GTP to RhoA enzyme" or "a compound that inhibits translocation of RhoA enzyme to the cellular membrane", or "a second compound which potentiates the effects of nitric oxide", and/or while the patient also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9^{th} ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of formula in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only those particular compounds of each functional groups are shown in the examples herein (see page 30 of specification for example). Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of the ingredients in the claimed method. See MPEP § 716.02(d).

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20, and 22-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitations "an organ subject" and “an individual” in claim 1 renders claims 1-20, and 22-25 indefinite. The recitations ""an organ subject" and “an individual” are not clearly defined in the specification. It is unclear as to the meaning of recitations "an organ subject" and “an individual” encompassed thereby.

The recitation, "a functional derivative" in claim 3 renders claim 3 indefinite. The recitation, "a functional derivative" is not clearly defined in the specification. Hence, one of ordinary skill in the art could not interpret the metes and bounds of the patent protection desired as to "a functional derivative" encompassed thereby.

The recitation, "others" in claim 12, and “certain drugs” in claim 25 renders claim 12 indefinite. The recitation"others" is not clearly defined in the specification. Hence, one of ordinary skill in the art could not interpret the metes and bounds of the patent protection desired as to "others" encompassed thereby.

The recitation, "potentiates" in claim 11 renders claim 11 indefinite. The recitation, " potentiates" is not clearly defined in the specification. Hence, one of ordinary skill in the art could not interpret the metes and bounds of the patent protection

desired as to "a second compound which potentiates the effects of nitric oxide" encompassed thereby.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 12 recites the broad recitation "a compound that acts on a downstream target of Rho-kinase" and the claim also recites "such as myosin light chain phosphatase,....and others" which is the narrower statement of the range/limitation. Claim 25 also recites "such as".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

> subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20, and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muro et al. (US 4,997,834, PTO-1449 submitted April 21, 2003) in view of the Merck Manual of Diagnosis and Therapy (17th ED) (page 1936-1837, PTO-892).

Muro et al. discloses that the compounds of formula (I) which has covered and encompassed the elected specie, Y-27632 (also known as (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, see abstract, col.2, col.8 lines 1-17 and 41-49) are useful in methods of treating hypertension and abnormal of smooth muscles (see col.1 lines 17-24) since these active compound possess coronary and cerebral blood flow-increasing activities (see col.8 lines 19-27). Muro et al. discloses the effective dose of the compound with a pharmaceutically acceptable carrier to be administered to a hypertensive male (see col.8 lines 53 to col. 10 line 25).

Muro et al. does not expressly disclose the employment of the particular Y-27632, in methods of treating male or female sexual dysfunction. Muro et al. does not expressly disclose the method further comprising the active agent herein.

The Merck Manual of Diagnosis and Therapy (17th ED) teaches that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can

result in erectile dysfunction (a known sexual dysfunction) (see page 1836 the right column). The Merck Manual of Diagnosis and Therapy (17th ED) also teaches that a nitric oxide is useful in treating erectile dysfunction or sexual dysfunction caused by vascular disorders.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular compound of Muro et al. in methods of treating male or female sexual dysfunction.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ ~~to employ~~ the particular compound of Muro et al. in methods of treating male or female sexual dysfunction, because the particular compound of Muro et al is known to be useful in methods of treating hypertension and abnormal of smooth muscles (see col.1 lines 17-24) since these active compound possess coronary and cerebral blood flow-increasing activities according to Muro et al. It is also known that hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction according to The Merck Manual of Diagnosis and Therapy (17th ED).

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compound of Muro et al., would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also

treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Moreover, one of ordinary skill in the art would have reasonably expected that combining the active agent herein such as guanine nucleoside dissociation inhibitor (GDI) as a compound that inhibits GTP binding to RhoA enzyme recited in claim 9, sodium nitroprusside as the compound recited in claim 10, NOR-1, known useful for the same purpose, i.e., inhibiting RhoA, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 1-20, and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshii et al. (PTO-892) in view of Uehata (EP 0 956 865, PTO-1449 submitted October 7, 2002) further in view of the Merck Manual of Diagnosis and Therapy (17th ED) (page 1936-1837, PTO-892).

Yoshii et al. discloses that the instant elected specie, Y-27632 (also known as (+)-(R)-trans-4-(1-aminoethyl)-N-(4-pyridyl) cyclohexanecarboxamide dihydrochloride monohydrate, see abstract) is the particular compound that attenuates RhoA kinase activity which can increase smooth muscle relaxation (see abstract). Yoshii et al. discloses that GTP is useful in combination with Y-27632 (see the abstract)

Yoshii et al. does not expressly disclose the employment of the particular Y-27632, in methods of treating male or female sexual dysfunction. Yoshii et al. does not expressly disclose the method further comprising the active agent herein.

Uehata (EP 0 956 865) discloses that the compounds of formula (III) which are structurally similar to Y-27632, as being RhoA kinase inhibitors, are useful in treating hypertension, vascular contraction, asthma in which smooth muscle contraction is involved and also treating fertilization and nidation of fertilized egg (see page 3 lines 13-20 and 30-34, page 8 lines 14-39).

The Merck Manual of Diagnosis and Therapy (17th ED) teaches that vascular disorders such as hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction (a known sexual dysfunction) (see page 1836 the right column). The Merck Manual of Diagnosis and Therapy (17th ED) also teaches that a nitric oxide is useful in treating erectile dysfunction or sexual dysfunction caused by vascular disorders.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular compound Y-27632 in methods of treating male or female sexual dysfunction.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ to employ the particular compound Y-27632 in methods of treating male or female sexual dysfunction, because Y-27632 is known to have RhoA kinase activity which can increase smooth muscle relaxation according to Yoshii et al.

Moreover, the compounds of formula (III) of Uehata which are structurally similar to Y-27632, are known RhoA kinase inhibitors, are also known useful in treating hypertension, vascular contraction, asthma in which smooth muscle contraction is involved and also treating fertilization and nidation of fertilized egg according to the Uehata patent. It is also known that hypertension, and diabetes mellitus, atherosclerosis, smooth muscle relaxation decreasing, and diminishing the amount of blood entering the penis, can result in erectile dysfunction according to The Merck Manual of Diagnosis and Therapy (17th ED).

Further, Y-27632 would be expected to have similar activity or property as those compounds disclosed in Uehata patent based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214.

Therefore, one of ordinary skill in the art would have reasonably expected that the particular compound Y-27632 would have beneficial therapeutic effects and usefulness in methods of treating male or female sexual dysfunction, by increasing coronary and cerebral blood flow- activities and smooth muscle relaxation, and also treating hypertension, and diabetes mellitus, atherosclerosis in patients suffering therefrom.

Moreover, one of ordinary skill in the art would have reasonably expected that combining the active agent herein such as guanine nucleoside dissociation inhibitor (GDI) as a compound that inhibits GTP binding to RhoA enzyme recited in claim 9,

sodium nitroprusside as the compound recited in claim 10, NOR-1, known useful for the same purpose, i.e., inhibiting RhoA, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
January 15, 2004